ATTACHMENT #3

STATEMENT OF WORK
PRECLINICAL TOXICOLOGY OF DRUGS DEVELOPED FOR CANCER PATIENTS

1. CONDUCT TOXICOLOGY AND PHARMACOLOGY STUDIES IN ACCORDANCE WITH THE COMPLETE PROTOCOL REQUIREMENTS THAT ARE DEVELOPED FOR EACH AGENT BY THE NCI COR.

It would be scientifically inappropriate to set rigid protocol guidelines that would be adequate for each compound that will be assessed, therefore, the guidelines below will be modified to account for data on the agent's *in vitro* cytotoxicity, biochemistry and schedule dependence as well as *in vivo* activity, if available. The types of studies that the Contractor will be directed to perform include, but are not limited to the following:

a. **Analytical Phase**: Drug identity analysis (*e.g.,* IR, NMR, MP, MS, or other emergent assay methodology designated by the Contracting Officers' Representative (COR), validation of the procedures supplied by the NCI for dose concentration analyses and validation of the requisite methodology for assay of drug in biological fluids shall be initiated immediately upon receipt of drug.

b. **Pharmacokinetic Phase**: Plasma elimination kinetics shall be determined in one or more of the following species: dogs, rodents and non-human primates after single intravenous doses of drug. Other routes of administration such as oral, intraperitoneal, subcutaneous and intramuscular may be necessary to evaluate as well. Bioavailability of non-parenteral routes and plasma clearance rates shall be determined in order to establish the dose required to produce effective drug concentrations in plasma for future toxicity studies. The ability of a drug to cross the blood-brain barrier shall be assessed in dogs or non-human primates.

c. **Screening and Preliminary Phase**: For each drug, establish a maximum tolerated dose (MTD) and dose limiting toxicities (DLT) in both beagle dogs and rodents. The use of non-human primates as an alternative species may be required for certain agents under evaluation.

The types of studies required in this phase shall be decided by the COR and may include the following:

i. Short-term toxicity studies in rodents
ii. Single or multiple dose range-finding studies in rodents, beagle dogs, or non-human primates.

d. **IND-Directed Toxicology Assessment Phase**: For each drug, establish toxicity and safety in relation to drug plasma concentrations or area-under-the-curve in both

beagle dogs and rodents. The use of non-human primates as an alternative species will be required for certain agents under evaluation. The types of studies required in this phase shall be decided by the COR and may include the following:

i. Single or multiple daily dose schedules such as Dx1, q3hr x 3, q8hr x 15, *etc*

ii. Continuous administration to mice via Alzet osmotic pumps and to beagle dogs, rats and non-human primates *via* infusion pumps for periods of from one hour up to 30 days.

iii. Twenty eight days or more of repeated administration of drug to rodents, beagle dogs and/or non-human primates

iv. Special studies such as cardiotoxicity, neurotoxicity, immunotoxicity may be requested as part of an existing study or in a separate study.

In actual practice, the complete evaluation of a promising therapeutic agent may require study designs that differ in complexity from the protocols provided. There may also be instances when studies on a drug will be terminated after the initial protocol. Conceivably, the laboratory may be required to perform a preliminary evaluation (one or two protocols) on a number of drugs prior to completely evaluating one drug for the purpose of filing an IND.

2. GENERAL AREAS OF WORK

The task orders issued under this contract will have the following objectives. The Contractor shall:

a. Validate the analytical methodology to quantify drug levels in dosing solutions, biological fluids, and tissues as required. Measure drug plasma levels in rodents, beagle dogs and/or non-human primates treated with the agent under study. Calculate and report all important pharmacokinetic parameters from the derived data.

b. Determine bioavailability of drug after oral and/or intraperitoneal, subcutaneous or intramuscular administration. Calculate and report all relevant pharmacokinetic parameters from the derived data.

c. Determine acute toxicity, (including, but not limited to, clinical observations, body weights, clinical pathology, histopathology) and plasma drug levels in rodents, beagle dogs and/or non-human primates over specified time periods.

d. Assess subacute toxicity (including, but not limited to, clinical pathology, hematology, histopathologic evaluation of tissues, clinical observations) in rodents, beagle dogs and/or non-human primates.

e. Assess cardiotoxicity, neurotoxicity, and immunotoxicity in rodents, beagle dogs and/or non-human primates as specified by the COR.

3. GOVERNMENT FURNISHED PROPERTY/SUPPLIES

a. Dogs, rats, rabbits, non-human primates and specialty animals such as cathetered rats will be purchased by the contractor under this contract as specified by the COR.

b. The Government will furnish the test articles and some of the control articles used in these studies.

c. Available analytical chemistry information including chemical identity data and methodology for dose concentration analysis, plasma drug analysis procedures, formulation information, available literature, *etc.* will be supplied by the Government.

d. Specialized equipment for infusion studies (pumps, jackets, collars, *etc*.) will be furnished by the contractor.

4. HUMAN SUBJECTS

It is hereby understood and agreed that **research involving human subjects shall not be carried out under this contract,** and that no material developed, modified or delivered by or to the Government under this contract, or any subsequent modification of such material will be used by the Contractor or made available by the Contractor for use by anyone other than the Government for experimental or therapeutic use involving humans without the prior written approval of the Contracting Officer. However, refuse human materials such as blood, serum, plasma, bone marrow, liver, kidney, other tissues, *etc.* may be necessary for use on this contract.

5. HUMAN MATERIALS

Human samples will be coded and anonymized such that the donors cannot be identified. The Contractor is responsible for any local IRB approvals required for work with human samples as described herein and for implementation of, and adherence to, all federal, local, and institutional policies regarding the occupational health and safety of personnel working with animal and/or human plasma, urine, or other tissues. Additionally, ship samples generated in-house or received externally to other laboratories at the request of the COR.

The acquisition and supply of all human specimen material used under this contract shall be obtained by the Contractor in full compliance with applicable State and Local laws and the provisions of the Uniform Anatomical Gift Act in the United States, and no undue inducements, monetary or otherwise, will be offered to any person to influence their donation of human material.

The Contractor shall receive written documentation that all human materials obtained as a result of research carried out by collaborating sites were obtained with prior approval by the Office for Human Research Protections (OHRP) of an Assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved Assurances, whether domestic or foreign, and compliance must be ensured by the Contractor.

Provision by the Contractor to the Contracting Officer of a properly completed "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption", Form OMB No. 0990-0263(formerly Optional Form 310), certifying IRB review and approval of the protocol from which the human materials were obtained constitutes the written documentation required. The human subject certification can be met by submission of a self designated form, provided that it contains the information required by the "Protection of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption", Form OMB No. 0990-0263(formerly Optional Form 310).

6. HEALTH AND SAFETY PLAN

Each agent will be considered potentially hazardous. Therefore, all necessary precautions must be taken to protect personnel and the environment against possible exposure to the agents being tested. The Contractor shall perform all work associated with this contract in accordance with all applicable Federal, State and local regulations including transportation and disposal of hazardous waste.

7. ACCESS TO DATA

The Government requires that all data accumulated under the projected contracts be immediately available for its review and those provisions are made to maintain confidentiality of all data. Authority to release data may be granted only by the Contracting Officer together with the COR and must be in writing.

All individual animal data should be provided to the COR in a format that allows integration into DTP databases. Excel or other tab delimited file formats for are acceptable. Other formats will be considered but compatibility shall be confirmed.

8. CONFIDENTIALITY OF INFORMATION

Certain data provided to the Contractor under this contract must be treated confidentially. The data to be treated confidentially is associated with certain Adiscreet compounds that are not available to the public. When compounds are assigned to the Contractor, these discreet compounds will be identified by the letter AD as a prefix to the compound NSC number. Under no circumstances are chemicals or drugs or any information associated with these chemicals or drugs to be released or divulged without prior written approval of the NCI COR.